REMARKS

The applicant requests that the examiner update the attorney docket number in this application as indicated above. The attorney docket number currently used by the examiner is that of a prior law firm no longer involved in current prosecution.

Further, the applicant notes that the status of claim 17 is not provided on the Office Action Summary. However, in view of the rejections made with respect to pending claims, and the fact that claim 17 does not recite a limitation on which the examiner based rejection of other claims, the applicant assume claim 17 is also allowable and request notification if this assumption is incorrect.

The rejection of claims under 35 USC §112, first paragraph

The examiner rejected claims 9 through 14 and 18 through 27 under 35 USC §112, first paragraph, for assertedly lacking enablement in the specification. More particularly, the examiner admitted that the specification is enabling of zinc, anti-angiogenic agents and anti-cancer agents, but assertedly "does not provide enablement for all compounds being different than tetraalkylammonium tetrathiomolybdate compound[[.]]" [Office Action, p. 2]. To purportedly support the rejection, the examiner first enumerated the considerations set out in *In re Wands* and discussed several of these factors stating,

(i) unpredictability of pharmaceutical and chemical art is high,

(ii) the claims are very broad and encompass a composition including any agent that is different from tetraalkylammonium tetrathiomolybdate,

(iii) the specification provides guidance only for and is enabled for adding angiogenic [sic] and anti-cancer agents,

(iv) the examples are drawn to the combination of tetraalkylammonium tetrathiomolybdate and zinc and a few anti-cancer drugs, and

(v) since compound structure and activity for such pharmaceutical use must be determined from case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue experimentation to obtain pharmaceutical compositions by adding an agent to tetraalkylammonium tetrathiomolybdate.

The applicants respectfully traverse.

When the nature of the invention is viewed with respect to the state of the prior art and the level of skill in the art, the applicants submit that the invention as claimed is enabled by the specification. Moreover, when what was known in the art at the time of the claimed priority date of the application is taken into consideration, the amount of guidance and number of working examples in the specification become minor considerations in the enablement analysis. Thus, when all of the *Wands* factors are properly considered, the amount of experimentation required to practice the invention is nothing more than routine and not undue.

The nature of the invention recited in the rejected claims can be described in simplest terms as a composition wherein the composition includes a tetraalkylammonium tetrathiomolybdate compound and another therapeutic agent. This "other" therapeutic agent may be another tetraalkylammonium tetrathiomolybdate as long as it is distinct from the first recited tetraalkylammonium tetrathiomolybdate, or it may be another therapeutic agent that is not a tetraalkylammonium tetrathiomolybdate. Accordingly, the recited composition has application in the treatment of a single indication or multiple indications with dissimilar therapeutics, i.e., combination therapy.

Regardless of the intended use, the invention contemplates tetraalkylammonium tetrathiomolybdate compositions including any of the multitude of other therapeutics well known and routinely used in the art, and in regard to this aspect of the state of the art prior to the priority date of the present application, the PHYSICIAN'S DESK REFERENCE, 56TH EDITION (2002[1], Medical Economic Group, Montvale NJ) (hereinafter "the PDR", the Forward of which is provided as Exhibit A lists over 3,200 pharmaceuticals which could be included in the claimed composition. This edition of the PDR also makes note of its co-published PDR PHARMACOPOEIA POCKET DOSING GUIDE which provides "FDA-approved dosing recommendations for over 1,500 drugs," as well as the PDR FOR HERBAL MEDICINE which provides "assessment of 700 botanicals." These compendia do not even include all of the therapeutic equivalents found in the US Department of Health and Human

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[1] The PDR typically publishes in the year prior to its copyright date. Thus the 2002 PDR published in 2001. If the examiner requests evidence of this fact, advice of the same is requested.

Services' APPROVED DRUG PRODUCT (also known as "the Orange Book," the Table of Contents and Preface are provided as Exhibit B) or the internationally approved drugs in USP DICTIONARY published by US Pharmacopeia (the Table of Contents and Preface are provided as Exhibit C). Thus, the state of the art at the time of the claimed priority date of the application was rife with information relating to a huge number of therapeutics along with dosing guidelines (and therefore composition production) any of which could be included in the recited composition as "a therapeutic agent different from said tetraalkylammonium tetrathiomolybdate compound," and the absence of this information from specification cannot be deemed detrimental in an analysis of the specification for enablement. The examiner is reminded that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The contribution to the art provided by the instant invention is, *inter alia*, the identified therapeutic usefulness of tetraalkylammonium tetrathiomolybdate compounds, notably absent from the prior art, and as such, an enabling specification need only provide guidance for use of compounds of this type without undue experimentation since use of other therapeutic compounds is enabled by knowledge common in the art. The specification teaches production of compositions using these compounds, and their use, which is sufficient for enablement. Indeed, the examiner admits the specification is enabling for tetraalkylammonium tetrathiomolybdate compound compositions (as further evidenced by the allowability of claim 1 and claims depending therefrom). The worker of ordinary skill is therefore left only to weave the common knowledge in the art into the present teachings as they relate to tetraalkylammonium tetrathiomolybdate to arrive at the invention as claimed. If it is stipulated that the level of skill in the art is high as generally accepted (*see In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)) (and if the examiner disagrees, the applicants request evidence to the contrary), it is submitted that the present specification would enable the worker of ordinary skill to utilize a tetraalkylammonium tetrathiomolybdate compound as disclosed and combine it in a composition with any of the numerous other known therapeutics well known in the art with no more than routine experimentation.

CONCLUSION

In view of the remarks made herein, the applicant believes that all claims are now in condition for allowance and request notification of the same.

Dated: April 16, 2007

Respectfully submitted,

By _____

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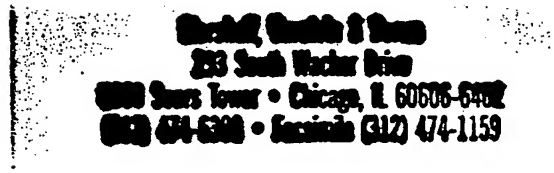

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ISBN: 1-56363-411-2

FOREWORD TO THE FIFTY-SIXTH EDITION

Welcome to the 2002 edition of *PDR*. With over 3,000 pages of detailed prescribing information approved by the FDA, this volume is unquestionably the healthcare community's most fundamental pharmaceutical reference—an indispensable source of in-depth data on the efficacy, potential adverse effects, clinical pharmacology, and proper use of thousands of prescription medications.

For complicated cases and special patient problems, there is certainly no better resource to turn to. In routine situations, however, a synopsis of the most important facts will often suffice. For just such occasions, *PDR* now offers the *PDR Pharmacopoeia™ Pocket Dosing Guide*. This handy little book can accompany you wherever you need to go, around the office or on rounds. Only slightly larger than an index card and a half-inch thick, it fits easily into any pocket, while providing you with FDA-approved dosing recommendations for over 1,500 drugs. Unlike other condensed drug references, it's drawn almost exclusively from the FDA-approved drug labeling published in *Physicians' Desk Reference*. And its tabular presentation makes lookups a breeze. At $9.95 a copy, it's a tool you really can't afford to be without.

Recently, the use of over-the-counter nutritional supplements has sky-rocketed, and *PDR* has responded with a brand new medical reference covering this unfamiliar—even exotic—set of agents. Entitled *PDR® for Nutritional Supplements™*, it offers the latest scientific consensus on hundreds of popular supplement products, including an array of amino acids, co-factors, fatty acids, probiotics, phytoestrogens, phytosterols, over-the-counter hormones, hormonal precursors, and much more. Focused on the scientific evidence for each supplement's claims, this unique new reference offers you today's most detailed, informed, and objective overview of a burgeoning new area in the field of self-treatment. To protect your patients from bogus remedies and steer them towards truly beneficial products, this book is a must.

For counseling patients who favor herbal remedies, another *PDR* reference may prove equally valuable. Now in its second edition, *PDR® for Herbal Medicines™* provides you with the latest science-based assessment of some 700 botanicals. Indexed by scientific, common, and brand names (as well as Western, Asian, and homeopathic indications) this volume also includes a Side Effects Index, a Drug/Herb Interactions Guide, an Herb Identification Guide with nearly 400 color photos, and a Safety Guide that lists herbs to be avoided during pregnancy and nursing and herbs to be used only under professional supervision. Although botanical products are not officially regulated or monitored in the United States, *PDR for Herbal Medicines* provides you the closest analog to FDA-approved labeling—the findings of the German Regulatory Authority's herbal watchdog agency, Commission E.

To maximize the value of *PDR* itself, you'll also need a copy of the 2002 edition of the *PDR Companion Guide™*, an 1,800-page reference that augments *PDR* with a total of 10 unique decision-making tools:

- **Interactions Index** identifies all pharmaceuticals and foods capable of interacting with a chosen medication.
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- **Cost of Therapy Guide** provides a quick overview of the relative expense of the leading therapeutic options for a variety of common indications.
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The *PDR Companion Guide* includes all drugs described in *PDR, PDR For Nonprescription Drugs and Dietary Supplements™*, and *PDR For Ophthalmic Medicines™*. We're certain that you'll find it makes safe, appropriate selection of drugs faster and easier than ever before.

PDR and its major companion volumes are also found in the *PDR® Electronic Library™* on CD-ROM, now used in over 100,000 practices. This Windows-compatible disc provides users with a complete database of *PDR* prescribing information, electronically searchable for instant retrieval. A standard subscription includes *PDR's* sophisticated search software and an extensive file of chemical structures, illustrations, and full-color product photographs. Optional enhancements include the complete contents of *The Merck Manual Seventeenth Edition, Stedman's Medical Dictionary,* and *Stedman's Spellchecker*. For anyone who wants to run a fast double check on a proposed prescription, there's also the *PDR® Drug Interactions and Side Effects System™* — sophisticated software capable of automatically screening a 20-drug regimen for conflicts, then proposing alternatives for any problematic medication. This unique decision-making tool now comes free with the *PDR Electronic Library*.

For more information on these or any other members of the growing family of *PDR* products, please call, toll-free, 1-800-232-7379 or fax 201-573-4956.

Physicians' Desk Reference is published by Medical Economics Company in cooperation with participating manufacturers. Each full-length entry provides you with an exact copy of the product's FDA-approved labeling. Under the federal Food, Drug and Cosmetics (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer for only those uses for which the drug's safety and effectiveness have been established. The Code of Federal Regulations 201.100(d)(1) pertaining to labeling for prescription products requires that for *PDR* content "indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions" must be *"same in language and emphasis"* as the approved labeling for the products. The Food and Drug Administration (FDA) regards the words *same in language and emphasis* as requiring VERBATIM use of the approved labeling providing such information. Furthermore, information that is emphasized in the approved labeling by the use of type set in a box, or in capitals, boldface, or italics, must be given the same emphasis in *PDR*.

The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling. For products that do not have official package circulars, the publisher has emphasized the necessity of describing such products comprehensively, so that physicians can have access to all information essential for intelligent and informed decision-making. Particularly in the case of over-the-counter dietary supplements, it should be remembered that this information has not been evaluated by the Food and Drug Administration, and that such products are not intended to diagnose, treat, cure, or prevent any disease.

The function of the publisher is the compilation, organization, and distribution of this information. Each product description has been prepared by the manufacturer, and edited and approved by the manufacturer's medical department, medical director, and/or medical consultant. In organizing and presenting the material in *Physicians' Desk Reference*, the publisher does not warrant or guarantee any of the products described, or perform any independent analysis in connection with any of the product information contained herein. *Physicians' Desk Reference* does not assume, and expressly disclaims, any obligation to obtain and include any information other than that provided to it by the manufacturer. It should be understood that by making this material available, the publisher is not advocating the use of any product described herein, nor is the publisher responsible for misuse of a product due to typographical error. Additional information on any product may be obtained from the manufacturer.

CONTENTS

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2000.

21ST EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
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2001

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVED DRUG PRODUCTS
with
Therapeutic Equivalence Evaluations

CONTENTS

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVED DRUG PRODUCTS
with
Therapeutic Equivalence Evaluations

PREFACE TO TWENTY FIRST EDITION

The publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the List), identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act). Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review [e.g., Donnatal® Tablets and Librax® Capsules] or pre-1938 drugs [e.g., Phenobarbital Tablets]) are not included in this publication. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products on the List is independent of any current regulatory action through administrative or judicial means against a drug product. In addition, the List contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the Act.

Background of the Publication. To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that it be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests in the late 1970s for FDA assistance in preparing both positive and negative formularies, it became apparent that FDA could not serve the needs of each state on an individual basis. The Agency also recognized that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. As a result, on May 31, 1978, the Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The List was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under the provisions of Section 505 of the Act.

The therapeutic equivalence evaluations in the List reflect FDA's application of specific criteria to the approved multisource prescription drug products on the List. These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. An explanation of the code appears in the *Introduction*.

A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582). The first publication, October 1980, of the final version of the List incorporated appropriate corrections and additions. Each subsequent edition has included the new approvals and made appropriate changes in data.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act (1984 Amendments). The 1984 Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The *Approved Drug Products with Therapeutic Equivalence Evaluations* publication and its monthly Cumulative Supplements satisfy this requirement. The *Addendum* to this publication identifies drugs that qualify under the 1984 Amendments for periods of exclusivity (during which ANDAs or applications described in Section 505(b)(2) of the Act for those drugs may not be submitted for a specified period of time and, if allowed to be submitted, would be tentatively approved) and provides patent information concerning the listed drugs which also may delay the approval of ANDAs or Section 505(b)(2) applications. The *Addendum* also provides additional information that may be helpful to those submitting a new drug application to the Agency.

The Agency intends to use this publication to further its objective of obtaining input and comment on the publication itself and related Agency procedures. Therefore, if you have comments on how the publication can be improved, please send them to the Director, Division of Data Management and Services , Office of Information Technology, Center for Drug and Evaluation and Research, HFD-90, 5600 Fishers Lane, Rockville, MD 20857. Comments received are publicly available to the extent allowable under the Freedom of Information regulations.

The authorized
list of established names
for drugs in the United States of America

2001 EDITION

USP DICTIONARY

of USAN and International Drug Names

Published in accordance with the directions of the
Expert Committee on Nomenclature and
Labeling of the USP Council of Experts,
with the cooperation of
the United States Adopted Names Council

U.S. Pharmacopeia
12601 Twinbrook Parkway, Rockville, MD 20852

This volume is dedicated with respect, appreciation, and gratitude to the memory of

LLOYD C. MILLER, Ph.D. (1907–1998)

Director of Revision of the U.S. Pharmacopeia from 1950 to 1970, whose recognition of the importance of devising unique nonproprietary names for drugs led to establishment of the USAN Council by the cosponsoring organizations

and

KURT L. LOENING, Ph.D. (1924–2000)

World renowned expert on chemical nomenclature and information, whose significant participation over many years gave assurance of complete and authoritative chemical information for the dictionary.

"Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in the *USAN and the USP Dictionary of Drug Names*." [21 CFR 299.4]

A compilation of the United States Adopted Names (USAN) selected and released from June 15, 1961, through November 30, 2000, current USP and NF names for drugs, and other nonproprietary drug names, the *USP Dictionary* incorporates the text previously published under the title *USAN and the USP Dictionary of Drug Names.*

Executive Vice President/Roger L. Williams

Library of Congress Catalog Card Number: sn 94001224
ISSN 1076-4275
ISBN 1-889788-08-2

U.S. Pharmacopeia
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Contents

Preface

The text of this dictionary of nonproprietary names, brand names, code designations, and Chemical Abstracts Service registry numbers for drugs has been published continually since 1963 by the United States Pharmacopeial Convention, Inc. (USP), as a public service and particularly to support the United States Adopted Names (USAN) program which began in 1961. It is prepared under the aegis of the USP Expert Committee on Nomenclature and Labeling.

37th Edition

This dictionary, now in its thirty-seventh edition, includes the thirty-seventh compilation of United States Adopted Names (for which the abbreviation, USAN, generally is used). It is cumulative from June 15, 1961, when the U.S. Adopted Names program began, through December 31, 2000, and thus provides the complete list of USAN released through the latter date. It incorporates the text of the publication previously known as *USAN and the USP Dictionary of Drug Names* and supersedes the 2000 edition and all earlier editions of the dictionary.

Supplements to the dictionary are published bimonthly in the *Nomenclature* section of *Pharmacopeial Forum* (*PF*), USP's Journal of Standards Development and Official Com pendia Revision. The new names and revisions of existing names in supplements are cumulatively included in the next published edition of the dictionary.

The Federal Food and Drug Administration (FDA) has stated that interested persons may, in the absence of the designation of an official name, rely on *USAN and the USP Dictionary of Drug Names* (now known as the *USP Dictionary of USAN and International Drug Names*) for the established name for any drug in the U.S.A. (see *FDA Established Names*). The FDA has indicated also that it will not routinely designate official names and will do so only under certain specific conditions.

The USAN and the current compendial—*United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*)—names are printed in **boldface** type. The International Nonproprietary Names (INN), British Approved Names (BAN) and Japanese Accepted Names (JAN), along with other miscellaneous names, appear in regular lightface type.

Included herein are 239 new U.S. Adopted Names released since publication of the previous edition of this book, as well as additions of other names for drugs. This edition reflects also hundreds of changes affecting information given in previously published entries.

The need for such compilations grows ever greater as the lists lengthen. The body of compounds in active use as drugs does not increase greatly, because new and better drugs tend to displace older drugs intended for the same purposes. On the other hand, new brand names may appear long after a drug is first marketed. The number of nonproprietary names increases steadily because, once assigned, a name remains on record and may not be reassigned even though the compound that it designates has been abandoned. Although rarely done, a brand name may be recycled and applied to another drug. Notable, too, are changes in the ingredients of combination drug products, while retaining the same brand name.

This book lists 9,234 nonproprietary drug name entries. These entries contain more than 4,281 brand names; 4,034 code designations (including 396 NSC numbers); and more than 10,069 CAS registry numbers. There are 7,984 graphic formulas depicted. The total number of USAN herein is 3,799.

All International Nonproprietary Names (INN) published by the World Health Organization from the start of the INN program in 1953 through 2000 are included in this book. Where an INN or other international name (BAN, JAN) exists for a drug that is covered by a **boldface** entry, the entry designates whether the INN, BAN, or JAN is the same as the corresponding USAN or *USP* or *NF* name or differs, in which case the difference is shown.

As is stated in this preface under *USAN Procedure*, there is increasing emphasis on the worldwide adoption of the same name for each therapeutic substance in view of the manifest advantages it offers to better communication and world trade. It is perhaps possible that the policy of including *all* INN in this dictionary may lend added perspective and eventually serve to reinforce that aim for more uniformity.

Appendixes, which follow the main alphabetic list, are included on (I) brand names for USAN and other nonproprietary names; (II) USAN and USP and NF names listed by categories; (III) molecular formulas; (IV) code designations for USAN and other nonproprietary names; (V) CAS registry numbers and NSC numbers; (VI) VA classification system; (VII) guiding principles for coining U.S. Adopted Names for drugs; (VIII) guiding principles for coining U.S. Adopted Names for contact lens materials; and (IX) USAN submission forms. Two appendixes that appeared in previous editions are not included in this 2001 edition of the dictionary. The former appendix on USAN for Technetium Tc99m radiopharmaceuticals, which merely duplicated the information found alphabetically in the main section of the dictionary under Technetium in only slightly modified form, has been eliminated. The former appendix that listed orphan drug products has also been eliminated; current and complete information is readily accessible on the internet (ref: www.fda.gov/orphan is the orphan drugs website, and www.fda.gov/cder/drug leads to FDA's Orange Book).

With respect to the legal status of trademarks cited as brand names herein, inquiries should be directed to the U.S. Patent Office.

The database of this dictionary has been composed by computer with storage and retrieval capabilities designed to facilitate future revisions and additions to the text as needed. Completeness and accuracy are of course paramount objectives in a compilation such as this. Suggestions of corrections or additions to the text will be welcomed for future consideration.

USP Expert Committee on Nomenclature and Labeling

In accordance with the Rules and Procedures of the 2000-2005 Council of Experts as adopted pursuant to the USP Bylaws, this dictionary is prepared under the aegis of the USP Expert Committee on Nomenclature and Labeling for 2000–2005, which currently comprises:

Loyd V. Allen, Ph.D.
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Herbert S. Carlin, D.Sc., *Chair*
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Rosemary C. Polomano, Ph.D., M.S.N., R.N.
Thomas P. Reinders, Pharm.D.
Eric B. Sheinin, Ph.D.
Philip D. Walson, M.D.

The USP Rules and Procedures provide that the Expert Committee on Nomenclature and Labeling "shall be responsible for promoting uniformity and consistency among official titles in the *USP* and the *NF* and the *USP DI*, coining suitable titles where such are needed because of the lack of public (nonproprietary) names or to improve the names already in use. The titles shall be in harmony with convenience in prescribing and with accepted tenets of general usage and shall be simple, useful, and clearly distinguishing and differentiating." They provide further that the Expert Committee on Nomenclature and Labeling shall determine the parameters of content, format, and style of the information contained in the dictionary, and shall receive and rule upon all questions and appeals for reconsideration of text prepared by USP staff and appearing in the dictionary. These charges to the Expert Committee on Nomenclature and Labeling represent no change from the responsibilities relative to drug nomenclature that have resided with the Pharmacopeia since its founding in 1820. The appointment of the Expert Committee on Nomenclature and Labeling in no way alters the way in which the USP organization as a sponsor of the USAN Council, or the USP Council of Experts, works closely and cordially with the USAN Council. Indeed, the Expert Committee on Nomenclature and Labeling is concerned with several areas not within the scope of the USAN Council, e.g., terminology for dosage-form monograph titles, dealing with the active-moiety concept, and other aspects of the language used in the prescription, dispensing, sale, or manufacture of drugs.

The Expert Committee on Nomenclature and Labeling is supported by the U.S. Pharmacopeia. Dr. Charles H. Barnstein, who serves the Committee as Secretary, is consultant to the USP Division of General Policies, Requirements, Nomenclature and Labeling and is that Division's liaison to the Nomenclature and Labeling Committee; Jymeann King similarly is USP Division of Information Development staff liaison to the Expert Committee on Nomenclature and Labeling. Dr. William M. Heller serves as a consultant to the Committee.

USAN Council

The three organizations that sponsor the USAN program, i.e., the American Medical Association, the American Phar maceutical Association, and the U.S. Pharmacopeia, do so through representation on the USAN Council. Members are appointed by their sponsors, subject to acceptance by the other sponsors. In addition, the three organizations jointly select a member-at-large. Members are appointed for one-year terms and may serve no more than ten consecutive terms.

In 1967, negotiations were completed to provide for participation by the U.S. Food and Drug Administration in the program as a means of consolidating the work of selecting suitable nonproprietary names for drugs on the part of the federal government and the existing Council. Thus, a liaison representative of the FDA sits on the Council. The roster of the Council for 2001, with member appointment or designation shown parenthetically, includes:

Daniel L. Boring, Ph.D., (FDA)
Everett Flanigan, Ph.D. (USP)
William M. Heller, Ph.D. (at large)
John E. Kasik, M.D., Ph.D., *Chair* (AMA)
Alice Jean Matuszak, Ph.D. (APhA)

The USAN Council was formed January 2, 1964, to succeed the AMA–USP Nomenclature Committee. It works mainly by correspondence, although consultation by e-mail and FAX is occasionally used and Council meetings generally are held twice a year.

The USAN Council Secretariat is located at the American Medical Association, and is housed in the AMA headquarters. Sophia V. Fuerst serves the Council as Secretary.Inquiries and communications pertaining to USAN should be addressed to Ms. Fuerst.[1]

USAN Review Board

Short of resort to the courts, there existed prior to 1961 no effective means of settling controversy stemming from differ ences of opinion concerning drug name selection. The gap was filled by the establishment of a formal mechanism by which disputes may be settled.

To give effect to the procedure, a six-member board has been established and is known as the USAN Review Board. Two members are appointed by each sponsoring organization for one-year terms, subject to indefinite renewal.

Recourse to the Review Board in settling disputes over selection of the names has been relatively rare; in fact, its services have been employed in only four cases to date. Participants agree at the outset that the determination of the USAN Review Board is final and beyond appeal.

The USAN Review Board for 2001 comprises:

Alan H. Kaplan, J.D., *Chair* (USP)
Donald R. Bennett, M.D., Ph.D. (AMA)
Stuart Feldman, Ph.D. (APhA)
Charles O. Rutledge, Ph.D. (APhA)

[1] Secretary, USAN Council, c/o American Medical Association, P.O. Box 10970, Chicago, Illinois 60610 [Telephone: (312) 464- 4046].

Jordan L. Cohen, Ph.D. (USP)
Lauren A. Woods, M.D., Ph.D. (AMA)

The USAN Review Board secretariat is supported by the U.S. Pharmacopeia. Joseph G. Valentino, J.D., serves the Board as Secretary.

USAN Program

The USAN program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs and certain other related agents (e.g., pharmaceutic aids, contact lens plastics, surgical materials). The name-selection process should be initiated when the drug enters the clinical investigation stage. Indeed, USAN are sometimes created for compounds that never come to be marketed as drugs.

It must be kept in mind that the adoption of a name is independent of clinical evaluation or acceptance by the medical profession of the article to which the name applies. Nevertheless, the USAN Council chooses each U.S. Adopted Name with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official *United States Pharmacopeia* or *National Formulary*.

The USAN program has earned a measure of prestige and world-wide recognition as an undertaking in the public interest. In addition to long-standing prejudices that work against instituting an orderly and effectual system of name selection, there also is widespread misunderstanding with respect to what constitutes good nonproprietary names and what purposes they serve. The USAN Council is committed to following estab lished principles for coining nonproprietary names (see Appendixes VII and VIII) and to enlisting the cooperation of the pharmaceutical industry in this country and of nomenclature groups abroad with a view to selecting a single, good nonproprietary name for each promising new drug.

The Purpose of USAN—A nonproprietary name of a drug serves numerous and varied purposes. Its principal functions are to identify the substance to which it applies and to serve as a designation that may be used without restriction by the public at large, both lay and professional. The importance of the latter function is enhanced by the restrictions necessarily imposed upon the nature and use of a trademark, particularly in the pharmaceutical field. Teaching in pharmacy and medicine requires a common designation especially for a drug that is available from several sources, or in a combination of two or more drugs. Nonproprietary names greatly facilitate communication between health professionals, and most journals demand their use. State formularies and hospital and managed care organization formularies generally use nonproprietary names as the titles of the articles recognized. A nonproprietary name is essential to the pharmaceutical manufacturer as a means of preserving trade mark rights to a brand name for the article concerned. Finally, federal law obliges the manufacturer to use the "established" nonproprietary name in advertising, labels, and brochures.

It is this wide variety of functions that makes difficult the task of expressing very exactly the criteria for judging simplicity and usefulness in drug names, attributes generally conceded to be desirable.

The Philosophy of the USAN Program—An examination of nonproprietary names for drugs currently in use is likely to result in an inaccurate evaluation of present nomenclature practices. Many of those names were coined prior to the adoption of systematized nomenclature procedures and principles. Indeed, many of those older names demonstrated the obvious need for an organized effort in the U.S. directed toward producing useful, simple and appropriate nonproprietary names for drugs. Existing names, then, reflect a mixture of old and new nomenclature practices and philosophy.

In many instances poor naming of drugs was due to the earlier practice of condensing the full chemical name into a chemically oriented nonproprietary name. At the time this practice came into being, the chemistry of most drugs was not too complex. With advancing chemical complexity of drug entities, however, nonproprietary names so derived became increasingly long and difficult to spell, pronounce, and remember.

In addition to the problems caused by the complexity of the word itself, chemically derived names have been criticized because they fail to provide useful information to anyone but a scientist involved in drug development. (Although the scientist's need is recognized, there exists more scientific and accurate chemical nomenclature to serve the purpose.)

Nonproprietary nomenclature is intended primarily for physicians, pharmacists, and those in related health professions concerned with the understanding of the drug's pharmacological and therapeutic properties. Therefore, it must be emphasized again that nonproprietary names should be coined in such a way as to be most useful to, and usable by, their primary users, i.e., those in the health professions.

USAN Procedure

A submission[2] for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America.

In the case of a substance that is regarded as an "Investiga tional New Drug" within the terms of the Federal Food, Drug, and Cosmetic Act of 1938, the process of selecting a USAN should be initiated preferably during the period of investigation when the substance is under clinical study so that the adoption of the USAN will be complete by the time the relevant New Drug Application is filed.

A submission for a USAN is expected to conform to the established Guiding Principles (see Appendixes VII and VIII) and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names.An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. WHA Resolution 46.19 and statements approved by the USAN Council, which address this concern regarding protection of USAN and INN, are included on pages 17 and 18 of the USAN *Handbook* (see below), fifth edition. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprie tary names for closely related drugs. Where the initial screening of the application suggests that the name fails to conform, or that it appears to conflict with an existing name, the USAN Council Secretary may offer suggestions with a view to expediting the selection process.

A user's fee for each U.S. Adopted Name is to be submitted with the form, "Request for a United States Adopted Name (USAN)," copies of which are included in this dictionary (see Appendix IX). Copies of the current

[2] Inquiries and submissions for USAN should be addressed to the Secretary, USAN Council, c/o American Medical Association, P.O. Box 10970, Chicago, Illinois 60610.

forms are obtainable on request from the Secretary of the USAN Council, or photocop ies of the forms may be submitted. Available on request from the Secretary of the USAN Council are copies of a U.S. Adopted Names (USAN) Council *Handbook*, which provides additional details regarding the Request forms and the application of the Guiding Principles.

Each application should be accompanied by the aforemen tioned appropriate form. This information, supplemented by the results of searches conducted by the Secretary, is referred to the Council members, whose views then are exchanged until a tentative decision can be submitted to the sponsor for comment. It should be emphasized that while the Council can ascertain the preferred chemical nomenclature for a structure claimed for any compound of definite composition, the Council is not in a position to confirm the structure or the claims for pharmacologic activity. The information given under the category Therapeutic Claim is based on the manufacturer's claims as submitted to FDA for investigational new drug approval or as approved by the firm for publication when the name is adopted. Adoption of a USAN does not imply endorsement of the claims or products by the USAN Council or its sponsoring organizations—the American Medical Asso ciation, the American Pharmaceutical Association, and the United States Pharmacopeia.

Suggested USAN are published in the *Trademark Bulletin of the Pharmaceutical Research and Manufacturers of America*, and in the USP publication, *Pharmacopeial Forum*,[3] and are also sent to the World Health Organization (WHO) nomenclature secretariat and to the Spanish regulatory authorities for review. These publications and reviews serve as invitations for comments or protests. No disclosure of the name of the sponsor or of the chemical nature of the substance appears in these statements.

Provided the sponsor consents, and in any case if there has been publication of the name elsewhere, the tentatively adopted USAN is then submitted for consideration to the World Health Organization. If no objections are raised, adoption is considered final and the USAN is published in a "New Names" section such as in *Clinical Pharmacology and Therapeutics*[4] and in the bi-monthly *Pharmacopeial Forum*.Copies of the new USAN lists are distributed widely to the American pharmaceutical press, with the expectation that the USAN will quickly receive wide publicity.

Despite the efforts to give notice of the proposed adoption of a USAN in the early stages and to exercise care in avoiding conflicts with established names, valid objections sometimes arise rather late. All such objections receive conscientious attention from the Council.

Occasionally, a USAN will be found unsuitable for adoption elsewhere, either internationally by the WHO or by one or more national bodies. Sometimes a closely similar name proves acceptable to one or more of these agencies, as in the case of the British Approved Name (BAN) "Cyclobarbitone" and its U.S. counterpart "Cyclobarbital." There is increasing emphasis, however, on the worldwide adoption of the same name for each therapeutic substance in view of the manifest advantages it offers to better communication and world trade.

Among the Guiding Principles for Coining U.S. Adopted Names for Drugs (see Appendix VII) is the principle that for most organic compounds, the designation for the pharmacolog ically active portion should appear first in the name; e.g., oxacillin sodium. This principle is applied generally in the entries herein.

FDA Established Names

Under the terms of the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, which became law October 10, 1962, the Secretary of Health and Human Services is authorized to designate an official name for any drug wherever deemed "necessary or desirable in the interest of usefulness and simplicity."[5]

The Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* regulations effective November 26, 1984, and elucidated February 16, 1988, which state, in part:

Sec.299.4 Established names of drugs.

(d)"...the Food and Drug Administration agrees with 'Guiding Principles for Coining U.S. Adopted Names for Drugs,' published in *USAN and the USP Dictionary of Drug Names....*"

(e)"The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common or usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names....*"[6] This dictionary incorporates the text previously published under the title, *USAN and the USP Dictionary of Drug Names*. It is to make absolutely clear which names are compendial (*USP* or *NF*) or common or usual (USAN) that this dictionary sets off the entries on these by showing them in **boldface** type.

International Nonproprietary Names

Under its charter, the World Health Organization (WHO) is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals (PINN; i.e., "Proposed International Nonproprietary Names"). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the PINN as a RINN ("Recommended International Nonpropri etary Name"), which almost all Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

International nonproprietary names selected during 1953–2000 are included herein.Some are identical to, and

[3] Published by the United States Pharmacopeia, 12601 Twinbrook Parkway, Rockville, Maryland 20852.

[4] Published by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Missouri 63141.

[5] F.D. & C. Act, Sec. 508 [358].

[6] 49 Fed. Reg. 37575 (1984) as amended by 53 Fed. Reg. 5369 (1988), amending 21 CFR 299.4.

identified with, USAN, *USP*, or *NF* entries; others are independent entries designated as INN. Where an INN is given in this volume as an independent entry, the chemical name and any graphic formula shown are generally those provided by the WHO.

International Cooperation

The USAN Council functions primarily to serve the health professions in the U.S. However, in an age when drug manufacturers market their products in many countries, when international travel is increasing steadily and medical and pharmaceutical literature is translated and read widely around the world, the need for cooperation regarding nomenclature activities among the major drug-producing countries clearly is evident.

In addition to the USAN Council, nomenclature agencies exist in Great Britain, France, Italy, Japan, the Nordic countries, Spain, Switzerland, and Russia. These agencies operate at varying levels of authority and cooperate with pharmaceutical manufacturers within areas of jurisdiction in the selection of appropriate nonproprietary names.

The agencies maintain liaison with one another in an effort to secure the wide adoption of the most appropriate and universally acceptable designation for each drug. The natural concern of each of the groups is with the drugs that are being synthesized, isolated, investigated, produced, or marketed in its own national area.

To prevent the confusion which arises when several nonproprietary names are used for a single drug, either in the same country or in several different countries, the WHO has assumed the responsibility of coordinating existing nomencla ture at the international level.

Through its Committee on Nonproprietary Names, whose members are drawn primarily from representatives of the national nomenclature agencies, the WHO has developed a procedure and formulated guiding principles for the selection of International Nonproprietary Names (INN). Where national nomenclature agencies exist, they usually act as agents for manufacturers by referring mutually selected designations (usually prior to national adoption) to the WHO with the request that these be considered for selection as INNs.

A manufacturer located in a country without a nomenclature agency can make a direct request for a nonproprietary name to the WHO or, in some instances, to an existing agency in another country, preferably one in which the pharmaceutical preparation is likely to be marketed.

After the selection of INNs, the WHO proposes and, in more favorable cases, recommends to all its member states that such names be adopted at the local level. Formal adoption in accordance with national practice is necessary to provide a review of the suitability of the INN for national use.

Pharmacy Equivalent Names

A Pharmacy Equivalent (PEN) name is a short and simple name that is offered by USP as a standardized and useful term that may be used for convenience by practitioners where it may be impractical to use the complete official monograph title of a compendial article.

The PEN name for a dosage form containing two or more therapeutic drug substances may be devised by combining portions of the official names of the component drug substances. A "Co-" prefix, not used elsewhere in compendial terminology, indicates that the article is a combination dosage form.For example, the PEN name Co-triamterzide is a representation of the *Co*mbination of *triamter*ene and hydrochlorothia*zide*.

PEN names are intended to be informative and to discourage the proliferation of trivial names and undefined abbreviations. Because a PEN name is not an official *USP* or *NF* title, it is not necessary that it appear on the label or in the labeling of a drug product.

FDA Orphan Drugs

Under the terms of the Orphan Drug Act[7] of 1983, the development and marketing of drug products expected to be of limited commercial appeal but potentially useful in relatively rare disease conditions are encouraged. When the FDA makes an orphan product designation, if the product has not already been approved for marketing for some other use, the name designated may not be the established or proper name approved by the FDA for the product if eventually approved or licensed for marketing.

The ultimate selection of a U.S. Adopted Name for an orphan drug may be based on special considerations that pertain to this rather select group of drugs.Therefore, where a USAN for an orphan drug appears to follow a more chemically oriented terminology than is customary for drug nomenclature generally, such instance is not to be regarded as a basis or a precedent for a future selection of a U.S. Adopted Name.

Chemical Nomenclature

A nonproprietary name (often referred to as a *generic* name) and a proprietary name (often referred to as a *brand name* or a *trademark*) serve different useful purposes, but neither is designed to provide precise information concerning the chem ical structure of the drug substance.To describe the chemical structure, a third type of name, i.e., a *chemical name*, is needed.

Chemical names tend to be complex and cumbersome; thus, although they may provide, for scientific and technical personnel, a complete, precise, and unambiguous description of the substance, they fail to constitute a concise, convenient designation that meets the day-to-day needs of the pharmacist, the physician, the patient, the jurist, and others functioning in related activities that involve pharmaceuticals. These latter needs are more appropriately served by nonproprietary names, of which USAN are primary examples.

For USAN entries pertaining to drugs that are strictly definable chemical substances (and the vast majority of single- entity drugs are of this type), two *chemical names* are usually included in each entry to provide such definition. Of the many chemical names that could be used, the ones selected for this compilation are those that have been used as the American Chemical Society's *Chemical Abstracts* (CA) index names; thus, fundamentally and advantageously, they all stem from the same basic system of chemical nomenclature and they function, through CA, as keys to the world's chemical literature.

The first of these two names usually is the inverted form of the systematic chemical name developed by Chemical Abstracts Service (CAS), in general accordance with the recommenda tions of the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry and Molecular Biology (IUBMB), and employed in the current issues of CA. The second name, generated in accordance with the recommendations of these

[7] Pub.L. 97-414.

scientific unions, is included in view of the general recognition that it is neither practical nor desirable to rely solely on the CA index names for all purposes of identification and reference. The inverted form of the first name is provided because it guides the user *directly* to the CA literature—since that is the style in which chemical substances are indexed in that literature. Conversion to the uninverted form of the name is readily accomplished. Thus:

Hydrazinecarboximidamide, 2-[-(2,6-dichlorophenoxy)ethyl]-, sulfate, (2:1)
becomes
2-[2-(2,6-Dichlorophenoxy)ethyl]hydrazinecarboximidamide sulfate (2:1).

Benzeneacetic acid, α-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, 8-oxide, hydrochloride, *endo*-(±)-
becomes
(±)-*endo*-α-(Hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl benzeneace tate 8-oxide hydrochloride.

This second name is given in uninverted form and is of a systematic type formerly used in CA; it is identical with, or closely resembles, the chemical name sanctioned and employed by the IUPAC and by the WHO.

These two types of chemical names differ primarily in that while the IUPAC names make generous use of nonsystematic and semisystematic (often referred to as *trivial*) names and qualifying terms, all of which impede electro-mechanical manipulation, the CAS names are more systematic for most substances. It is primarily by virtue of this stricter adherence to systematic nomenclature that the CAS chemical names are more readily amenable to the ever-increasing demand for electronic processing by various means, thus greatly facilitating literature searches and the processing of other queries based on chemical composition described in terms of nomenclature.

A third chemical name is occasionally supplied in an entry herein, especially in instances where that name is of a type that has become firmly established through long-continued use, e.g., see bolasterone; calcium glubionate; panthenol; and taleranol. Also, a CAS chemical synonym is occasionally supplied as an additional name in the relatively rare instances where the CA index name for a chemical substance is not a chemical name, e.g., see cosyntropin; pepstatin.

[NOTE—The foregoing does not apply to chemical names shown for entries other than USAN and current compendial names established before the USAN program began. In those other entries, any chemical name shown, whether conforming to CAS nomenclature or otherwise, is given only for descriptive purposes to help identify the substance. The chemical name shown in an independent INN entry is usually that provided by the WHO.]

Identification of Names by Number

To meet the need for rapid handling of data on drugs for many purposes, compounds and preparations are being identi fied by number. This trend in no way minimizes the importance of adopting the best possible nonproprietary names for drugs; indeed, its success is related to the soundness of the names program, to the end that taken together the nonproprietary name and the number(s) assigned to it provide increasingly effective control of data and information on drugs.

In the system developed and being used by the CAS, registry numbers are assigned to compounds at random, and although unique, the numbers convey no compositional or other kinds of information. The FDA maintains the National Drug Code Directory, in which a three-part number is assigned to identify the manufacturer or distributor or repackager, the drug product, and the package. Other numerical classifications exist for literature searching.

In this book USAN entries and other entries, such as from current or former revisions of the *USP* and the *NF*, carry CAS registry numbers. A given entry usually carries only one such number, but because of (a) variations in the way in which information is reported in the literature, and therefore stored in automated files, and (b) the variety of searches expected to be conducted on such files, sometimes two, or occasionally more, CAS numbers are pertinent to a single entry. For example, information on the pharmacology of ampicillin may be stored in a file under either ampicillin anhydrous or ampicillin trihydrate, depending on how it was reported in the literature, and each of these substances carries its own CAS registry number. Similarly, information on the synthesis of doxorubicin hydrochloride may be stored under that entry or under the parent substance, doxorubicin.

With entries carrying multiple CAS registry numbers, the one carrying no annotation enclosed within brackets (usually the first one) is the registry number assigned to that entry. Each additional number is followed by a bracketed term which, as is apparent from the following examples, discloses its relationship to the assigned number. Prominent categories of entries carrying more than one CAS registry number are exemplified in the following:

Hydrated substances carry one registry number for the hydrate and another one for the anhydrous substance. Examples:
Theophylline 5967-84-0; 58-55-9 [anhydrous]
Ampicillin 69-53-4; 7177-48-2 [trihydrate]

Addition salts of organic bases carry one registry number for the salt and another one for the organic base. Examples:
Promethazine Hydrochloride 58-33-3; 60-87-7 [promethazine]
Acetophenazine Maleate 5714-00-1; 2751-68-0 [acetophenazine]

Quaternary salts carry one registry number for the salt and another one for the quaternary radical, if that radical has had a number assigned to it by CAS. Examples:
Bretylium Tosylate 61-75-6; 59-41-6 [bretylium]
Choline Chloride 67-48-1; 62-49-7 [choline]

Metal salts of uncommon organic acids and all salt-like substances carry one registry number for the salt and another one for the acid or acidic substance. Examples:
Edetate Sodium 64-02-8; 60-00-4 [edetic acid]
Hexobarbital Sodium 50-09-9; 56-29-1 [hexobarbital]

Entries for which CAS has replaced a registry number with another one carry both numbers, as recommended by CAS since the replaced number was in use prior to its replacement. Examples:
Aspartocin 4117-65-1; 1402-89-7 [replaced]
Phendimetrazine Tartrate 50-58-8; 21102-82-9 [replaced]; 634-03-7 [phendimetrazine]

In general, when using CAS registry numbers as search terms, all numbers *deemed pertinent* to the search at hand should be used. To omit one or more of such numbers is to risk failing to retrieve all of the stored information pertinent to the search. This does not mean that all of the registry numbers associated with a substance in this book must always be used in searches involving that substance. According to the nature of the query that has prompted the search, one can decide whether one or more of the registry numbers are not pertinent and can therefore be omitted.

Appendix V provides a tabulation of entries in the order of increasing CAS registry number.This is followed by a similar tabulation in the order of increasing NSC (National Service Center of the National Cancer Institute, National Institutes of Health) number; the corresponding NSC numbers are also in the respective individual entries.

Graphic Formulas

Consonant with the employment of Chemical Abstracts nomenclature, and also in the interest of uniformity of style, the orientation of ring systems and the depiction of stereoiso meric features in graphic formulas are generally consistent with CAS practices. Either alternating double bonds or a circle within a hexagon is used in graphic formulas to represent the bonding in benzene rings and all others that contain six atoms of any kind that are connected in conjugate (Kekulé) style in one or more of the individual resonant structures that contribute to the hybrid structure actually present in the molecule.

Many structures depicted in the dictionary were drawn by hand. All the USP and NF graphic formulas contained herein were drawn electronically to achieve a consistent style and uniform format.The existing hand-drawn structures were converted to bit-mapped images in the Tagged Image File Format (TIFF) that were then converted with commercial structure-recognition software to display the structure.

Molecular Weights

The standard atomic weights of the elements that are used in the tabulation of molecular weights are those recommended in 1997 by the IUPAC Commission on Atomic Weights and Isotopic Abundances. The exact atomic weights are used in the computations.The molecular weights derived from these atomic weights are systematically rounded off to two decimal places using the method adopted by the Executive Committee of the USP Division of General Policies, Requirements, Nomenclature and Labeling. That is, retain only the number to include the digits in the first three decimal places of the sum of the atomic weights:discard the last digit if it is smaller than 5 to obtain the molecular weight or discard the last digit if it is 5 or larger and increase the digit in the second decimal place by one to obtain the molecular weight.

Pronunciation Guide

Although to some extent the pronunciation is a subjective attribute and universal agreement would be but a vain hope, a simple guide, based on English-language spelling, on a limited scale is provided for many of the nonproprietary names herein. Inasmuch as slight differences in phonetics are regarded as relatively unimportant, no attempt is made to give a highly sophisticated system of diacritical marks. [NOTE—The pronun ciation guide is not repeated if the guide has been given for the same word in a prior entry.] In any event, comments will be welcomed with respect to instances where an alternative pronunciation is preferred in a particular area.

Radioactive Pharmaceuticals

Since the radioactive pharmaceuticals are specially packaged in distinctive containers, labeled with the internationally recognized symbols for radioactivity, and available only to specially trained personnel, the USAN Council has agreed on the general principle that for these drugs the nonproprietary name should include the name of the basic compound serving as the carrier for the radioactivity, the symbol for the radioactive isotope, and the atomic weight (inasmuch as several radioactive isotopes of a given element may be in use).

Brand Names

Brand names in use in the United States for the compounds listed are generally shown. The inclusion of these brand names herein is not to be regarded as indication that the names necessarily have been registered with the U.S. Patent Office.

The information on brand names included in this volume came from earlier editions, current literature sources, the USAN Council Secretariat, and a recent survey of participating manufacturers. No attempt is made to be exhaustive with respect to the inclusion of brand names. As a general principle, emphasis is on listing brand names of those domestic firms that have participated in the USAN program by sponsoring one or more compounds for which USAN have been selected. The inclusion of various brand names bears no relationship to, and is not intended to affect, any brand interchange requirements.

It should be noted that the pharmacologic and/or therapeutic category stated in an entry may not necessarily apply to every brand name listed in that entry; e.g., the category may pertain to one or more dosage forms whereas a particular brand name may represent such dosage form(s) or perhaps some other dosage form not contemplated by the stated category.

The formulator and labeler of a drug product are not necessarily the same firm. However, sometimes a single formulator produces a drug product for several labelers and sometimes a single labeler purchases a drug product from more than one formulator. There is no general effort to make in this book a distinction between the formulator and the labeler of a product.

Code Designations

Alphanumeric combinations frequently are used during the investigational phase required to demonstrate the utility of new, potentially therapeutic substances. The alphabetic portion of a code designation usually is identifiable with the institution or firm that assigns the code designation to the agent under test. For example, among the code designations commonly encountered are some that include the initials "NSC." Code designations find their way into the scientific literature because it is customary to use them in identifying the compounds in early publications prior to adoption of a USAN.

Summary of Types of Information Provided

The individual entries in this volume comprise, in general, the following: (1) USAN (in **boldface** type), with year of its adoption in brackets; (2) official names (usually of the drug substances as distinct from the dosage forms) from the current revisions of the *United States Pharmacopeia* and the *National Formulary* (in **boldface** type), with some exceptions, e.g., combinations; (3) names that were official in previous revisions of the *USP* and the *NF*; (4) international and other nonpropri etary names; (5) miscellaneous older names that had been in general use at various times in the past; (6) brand names; and (7) code designations.

The statement of claimed pharmacologic and/or therapeutic activity is italicized in USAN entries and in entries

for current *USP* and *NF* names. In the case of many new entries, the sponsors of the USAN may not have complete information insofar as all of the categories of activity are concerned. Comments aimed toward the attainment of greater uniformity and usefulness in the pharmacologic classification system used herein will be welcomed, particularly if they are supported by authoritative information.

Literature references (e.g., "MI" for Merck Index) are given in some entries solely as sources of possible further information about the compound and do not imply any connection with the program for selection of nonproprietary names.

The names of the manufacturers currently or formerly concerned with the respective compounds are mentioned. Mergers and name changes of manufacturers and sales of brand names from one manufacturer to another are common. Where known, the name of the current owner of the brand name is given, but no special attempt is made to be up to date in all entries. Information that a manufacturer is no longer concerned with a compound will be gratefully received.

Further analysis of the content of this edition is given under *How to Use This Book*, on the inside front cover.

Acknowledgments

Sophia V. Fuerst, Sandra Van Laan, Stephanie Shubat, and Ruth Rivero of the USAN Council Secretariat, and Dr. Ruta Freimanis, who served as secretary to the Council through January 31, 2000, and, likewise Dr. Sabine Kopp-Kubel, Quality Assurance-INN, World Health Organization (WHO), continued to render invaluable assistance during the preparation of this book.Dr. Kurt L. Loening,* Topterm, and Dr. Sabine Kuhn, Chemical Abstracts Service, made significant contributions with their help on the graphic formulas and CAS registry numbers, and in providing chemical names consistent with the *Chemical Abstracts* conventions. Don L. Barker, Spectrum Computer Services, Inc., provided skillful database analyses and programming. Also assisting commendably in the production of this edition were USP staff personnel Susan L. Entwistle, Senior Project Manager; Deborah R. Miller, Supervisor, Publishing Technologies; Lauren T. Davis, Electronic Publications Specialist; Debbie James, Senior Publications Specialist; Sung Park, Graphic Designer and Beryl Voigt, Coordinator, Research and Development Laboratory.

Each of these individuals contributed significantly to this book. They all generously provided their expert knowledge, expeditious cooperation, and patience.Their contributions are sincerely appreciated.

Much of the work on the USAN program is hidden from view. The results, however, are shared by many, all of whom thus benefit from the labors of the few who give freely of time and effort and of others whose cooperation makes success possible. The continued willing cooperation from all segments of the pharmaceutical industry, which contributes immeasurably to the success of the USAN program as well as provides helpful information on the various entries throughout this book, is gratefully recorded.

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